Approaches to Determining Internal Dose in Inhalation Risk Assessment at the US EPA

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In risk assessment, the respiratory tract is characterized as a complex target system. Inhalation exposure to toxic compounds (vapors and gases) may lead to both portal-of-entry and systemic effects. In addition, the estimated risk to humans is generally based on data from animal studies. Several dosimetric approaches exist to estimate the internal or delivered dose to a target site from an inhalation exposure. These approaches vary in a continuum or hierarchy from default (e.g., set formula/equations) to optimal (e.g., computational fluid dynamics [CFD], physiologically based pharmacokinetic models [PBPK]) depending upon the amount of chemical-specific and species-specific information available. One approach is outlined in US EPA's *RfC Methodology* (EPA/600/8-90/066F/October 1994). In this approach (data-limited), the ratio of the ventilation rate (V_E) to the surface area (SA) of the respiratory tract region of interest, of the animal to the human [$(V_E/SA)_A/(V_E/SA)_H$], is used as an internal dose surrogate, assuming maximal absorption and uniform distribution. However, when more data are available, CFD, PBPK, or CFD–PBPK hybrid dosimetry models are used. CFD (air phase) models estimate the regional dose or flux (rate of transport) into tissue in both animals and humans and suggest that absorption is localized and non-uniform. PBPK models incorporate data on tissue-phase kinetics to estimate the tissue dose. Interspecies, hybrid CFD–PBPK models incorporate both air-phase and tissue-phase data to estimate tissue dose providing a comprehensive description of a chemical's disposition. It is anticipated that an analysis of the results from the CFD, PBPK, and hybrid models will help inform the data-limited approaches.

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